SYNTHESIS OF DEOXYAZEPINOMYCIN

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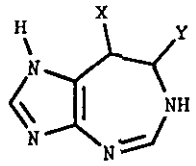
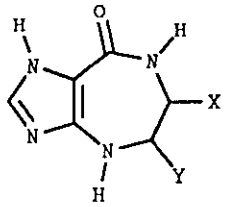
Abstract - The syntheses of several new derivatives of imidazo[4,5-e][1,4]diazepin-8-one are described.

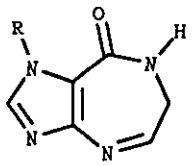
Several hydroxyimidazodiazepines have been isolated from bacterial cultures in recent years and they have been shown to inhibit enzymes involved in the metabolism of purines.[1-5] The best known of these compounds are coformycin[1] and pentostatin,[2] which are nucleosides derived from 8-hydroxyimidazo[4,5-d][1,3]diazepine (**1**). They have significant



(1) X = OH, Y = H
(2) X = H, Y = OH



(3) X = OH, Y = H
(4) X = H, Y = OH
(5) X = Y = H



(6a) R = Me
(6b) R = Bn

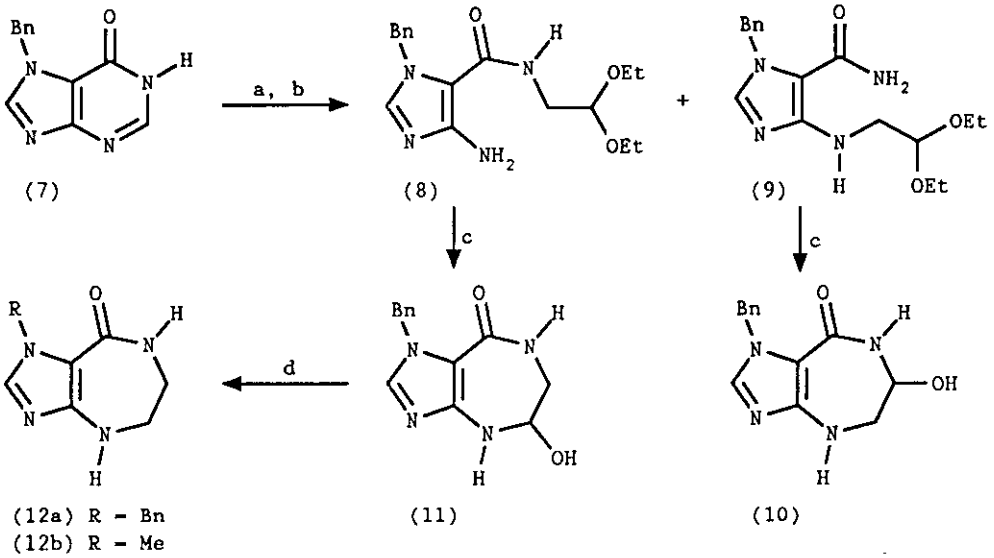
pharmacological potential as they are potent inhibitors of adenosine deaminase.[3] Derivatives of the isomeric 7-hydroxyimidazo[4,5-d][1,3]-diazepine (**2**) are also inhibitors of this enzyme.[4] Azepinomycin (**3**) is an inhibitor of guanine deaminase.[5] All of these analogs are effective because they mimic the transition states for the reactions catalyzed by

the enzymes they inhibit. We have been interested in preparing the azepinomycin isomer, 5-hydroxyimidazo[4,5-e][1,4]diazepin-8-one (**4**), and in light of a recent communication[6] reporting the synthesis of the nucleoside derivative of **4**, we are prompted to report our work in this area, including the first synthesis of deoxyazepinomycin (**5**).

There has been considerable interest in the synthesis of imidazo[4,5-e]-[1,4]diazepines in recent years.[7-13] The usual approach is the ring closure of an appropriately substituted aminoimidazolecarboxamide. The aminal function in azepinomycin has been realized by aqueous acidic hydrolysis of an acetal,[13] and we anticipated that a similar approach could be used for the preparation of the azepinomycin isomer (**4**). This approach was apparently successful for the nucleoside,[6] although it has been reported that an imine (**6a**) was formed when a related acetal was similarly treated with anhydrous trifluoroacetic acid.[10] We elected to attempt to use a benzyl group to protect the imidazole ring, and to prepare the necessary intermediate from the readily available 7-benzyl-hypoxanthine (**7**), as we had done for the synthesis of the related imidazo[4,5-e][1,4]diazepine-5,8-diones.[12]

7-Benzylhypoxanthine (**7**) was treated with sodium hydride and bromoacetaldehyde diethyl acetal to give a mixture of the 1- and 3-alkylated products, which were not separated but were subjected to ring opening with sodium hydroxide to give two imidazoles (**8** and **9**) in a 3:1 ratio. The imidazoles were separated by column chromatography and crystallized from ether. The major product was expected to be **8** since it results from alkylation of 7-benzylhypoxanthine at N-1. This was confirmed by proton nmr spectroscopy. The major product (**8**) has a broad two-proton singlet at 5.05 ppm assigned to the unsubstituted 4-amino group, while the minor product (**9**) has a one-proton triplet at 5.7 ppm assigned to the substituted 4-amino group. Further confirmation was

obtained by converting **9** to azepinomycin (**3**). Hydrolysis of the acetal function in aqueous acid gave the intermediate (**10**), from which the benzyl group was removed by catalytic hydrogenolysis.

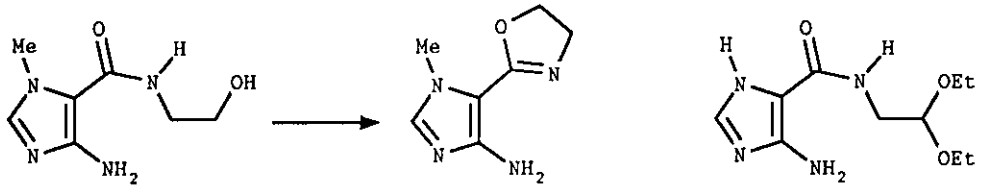


Reagents: a) NaH/$BrCH_2CH(OEt)_2$; b) NaOH; c) aq HCl; d) H_2/10% Pd-C

We expected to prepare **4** from **8** by an analogous series of reactions. Acid hydrolysis of **8** did indeed give the expected 1-benzyl-5-hydroxy-imidazo[4,5-*e*][1,4]diazepin-8-one (**11**). The structure of this compound was confirmed by one and two dimensional nmr spectroscopy. Both the amine proton (H-4) and the hydroxy proton were observed as doublets due to coupling with H-5, and the amide proton (H-7) appeared as a doublet of doublets due to coupling to the two non-equivalent protons at C-6. In contrast to the results with the 6-hydroxy isomer (**10**), reduction of the aminal functional group in the seven-membered ring of **11** was observed to take place during catalytic hydrogenolysis of the benzyl group. Using 10% palladium-on-carbon in acetic acid, 1-benzylimidazo[4,5-*e*][1,4]diazepin-8-one (**12a**) could be obtained in excellent yield. The nmr spectrum of **12a** includes a broad triplet at 6.35 ppm assigned to H-4, confirming that the

seven-membered ring has not been opened during the reaction. No conditions could be found in which the benzyl group was removed without reduction of the aminal. It is probable that reduction of **11** to **12a** proceeds *via* the imine (**6b**). Dehydration of **11** is apparently more facile than dehydration of **10**. Proton nmr of a sample of **11** stored in DMSO-d_6 at ambient temperature for 24 h shows a new set of signals consistent with **6b**,[14] while the spectrum of **10** is unchanged. Dehydration would be expected to be even faster in acetic acid. Further hydrogenolysis of **12a** over palladium hydroxide resulted in removal of the benzyl group to give imidazo[4,5-e][1,4]diazepin-8-one (deoxyazepinomycin) (**5**), which could also be obtained directly from **11** under similar conditions.

A compound assigned the structure **12b** was recently reported to result from the ring closure of **13**.[15] The nmr spectrum of this compound obtained in



(13) (14) (15)

CF_3CO_2D reportedly shows two triplets at 3.9 and 4.8 ppm. Exchangeable protons are not observed under these conditions. When the spectrum of **12a** is obtained under similar conditions the four protons at C-5 and C-6 are observed as a singlet at 3.75 ppm. On the basis of this evidence we consider it highly likely that the compound actually obtained from **13** is the oxazolidine (**14**), and not the diazepine (**12b**). There is considerable literature precedent for cyclization to five rather than seven-membered rings in related systems.[16]

In an attempt to prepare the unprotected hydroxy compound (**4**), we removed the benzyl group from the acetal (**8**) to give **15**. Acidic hydrolysis of **15** resulted in a complex mixture, in which **4** was observed by nmr as a minor

component (less than 10%) which could not be isolated. Apparently the free imidazole ring nitrogen is a more effective nucleophile than the amino group, making preparation of **4** by this route impractical.

EXPERIMENTAL

4-Amino-1-benzyl-N-(2,2-diethoxyethyl)imidazole-5-carboxamide (8) and **4-(2,2-Diethoxyethylamino)-1-benzylimidazole-5-carboxamide (9)**. To a solution of 7-benzylhypoxanthine (9.0 g, 40 mmol)[12] in DMF (120 ml) were added sodium hydride (60%, 1.8 g, 45 mmol) and bromoacetaldehyde diethyl acetal (6.5 ml, 43 mmol). The mixture was heated at 70°C for 16 h then cooled and concentrated *in vacuo*. The residue was partitioned between water and ethyl acetate, and the organic extracts were dried over magnesium sulfate and concentrated. The residue was dissolved in 95% ethanol (200 ml), 6 M aqueous sodium hydroxide (20 ml) was added, and the solution was heated under reflux for 2 h. The solvent was evaporated and the residue was partitioned between water and ethyl acetate. The organic extracts were dried over magnesium sulfate, concentrated, and chromatographed on silica, eluting with 0 - 4% ethanol in ethyl acetate. **9** (2.0 g, 15%) eluted first and crystallized from ether, mp 142-144°C. Anal. Calcd for $C_{17}H_{24}N_4O_3$: C: 61.42; H: 7.28; N: 16.86. Found: C: 61.53; H: 7.11; N: 16.84. Proton nmr (DMSO-d_6, 300 MHz): 1.09 (t, J = 7 Hz, 6H, $OCH_2C\underline{H}_3$), 3.28 (t, J = 6 Hz, 2H, $NHC\underline{H}_2CH$), 3.45 (dq, J = 7 Hz and 10 Hz, 2H, $OC\underline{H}_2CH_3$), 3.61 (dq, J = 7 Hz and 10 Hz, 2H, $OC\underline{H}_2CH_3$), 4.56 (t, J = 6 Hz, 1H, $NHCH_2C\underline{H}$), 5.39 (s, 2H, $PhC\underline{H}_2$), 5.70 (t, J = 6 Hz, 1H, $N\underline{H}CH_2CH$), 6.71 (br s, 2H, $CON\underline{H}_2$), 7.07 - 7.33 (complex, 5H, Ph), 7.61 (s, 1H, H-2). **8** (6.0 g, 45%) eluted later and crystallized from ether, mp 83-84°C. Anal. Calcd for $C_{17}H_{24}N_4O_3$: C: 61.42; H: 7.28; N: 16.86. Found: C: 61.44; H: 7.32; N: 16.95. Proton nmr (DMSO-d_6): 1.09 (t, J = 7 Hz, 6H, $OCH_2C\underline{H}_3$), 3.20 (t, J = 6 Hz, 2H, $NHC\underline{H}_2CH$), 3.40 (dq, J = 7 Hz and 10 Hz,

2H, OCH_2CH_3), 3.56 (dq, J = 7 Hz and 10 Hz, 2H, OCH_2CH_3), 4.47 (t, J = 6 Hz, 1H, $NHCH_2CH$), 5.03 (s, 2H, NH_2), 5.39 (s, 2H, $PhCH_2$), 7.10 - 7.31 (complex, 6H, Ph and CONH), 7.58 (s, 1H, H-2).

1-Benzyl-5-hydroxy-4,5,6,7-tetrahydroimidazo[4,5-e][1,4]diazepin-8(1H)-one (11). Compound (**8**) (4.65 g, 14 mmole) was dissolved in 1 M hydrochloric acid (420 ml). After 2 h, 2 M sodium hydroxide (210 ml) was added. The crystals that resulted were filtered, washed with water, and dried (3.02 g, 84%), mp >170°C (decomp.). Anal. Calcd for $C_{13}H_{14}N_4O_2$: C: 60.45; H: 5.46; N: 21.69. Found: C: 60.53; H: 5.39; N: 21.91. Proton nmr (DMSO-d_6): 2.85 (dd, J = 4 Hz and 14 Hz, 1H, H-6), 3.12 (ddd, J = 5 Hz, 7 Hz, and 14 Hz, 1H, H-6'), 4.88 (ddd, J = 5 Hz, 5 Hz, and 6 Hz, 1H, H-5), 5.26 (d, J = 15 Hz, 1H, PhCH), 5.32 (d, J = 6 Hz, 1H, OH), 5.64 (d, J = 15 Hz, 1H, PhCH'), 7.02 (d, J = 5 Hz, 1H, H-4), 7.08 (dd, J = 4 Hz and 7 Hz, 1H, H-7), 7.12 - 7.32 (complex, 5H, Ph), 7.64 (s, 1H, H-2).

1-Benzyl-4,5,6,7-tetrahydroimidazo[4,5-e][1,4]diazepin-8(1H)-one (12a). Compound (**11**) (2.6 g, 10 mmol) was dissolved in acetic acid (100 ml). Palladium-on-carbon (10%, 1 g) was added and the mixture was shaken under 40 psi of hydrogen for 6 h. The reaction mixture was filtered, the filtrate was concentrated, and the residue was treated with aqueous sodium bicarbonate. The product was filtered, and a second crop was obtained by extracting the aqueous filtrate with chloroform. The combined fractions were crystallized from 95% ethanol, yielding 2.2 g (92%), mp 190-192°C. Anal. Calcd for $C_{13}H_{14}N_4O$: C: 64.44; H: 5.82; N: 23.13. Found: C: 64.77; H: 5.88; N: 23.10. Proton nmr (DMSO-d_6): 3.12 - 3.18 (complex, 4H, NCH_2CH_2N), 5.45 (s, 2H, $PhCH_2$), 6.35 (br t, 1H, H-4), 7.12 - 7.31 (complex, 6H, Ph and H-7), 7.60 (s, 1H, H-2).

4,5,6,7-Tetrahydroimidazo[4,5-e][1,4]diazepin-8(1H)-one (5). Compound (**12a**) (0.72 g, 3 mmol) was dissolved in ethanol (50 ml). Palladium hydroxide on carbon (20%, 1 g) was added and the mixture was shaken under 40 psi of

hydrogen at 50°C for 4 h. The reaction mixture was filtered, the filtrate was concentrated, and the residue was crystallized from ethanol, yielding 0.41 g (90%), mp 220°C (decomp.). Anal. Calcd for $C_6H_8N_4O$: C: 47.36; H: 5.30; N: 36.83. Found: C: 47.03; H: 5.22; N: 36.89. Proton nmr (DMSO-d_6): 3.20 (s, 4H, $NC\underline{H}_2C\underline{H}_2N$), 6.29 (br s, 1H, H-4), 7.29 (br s, 1H, H-7), 7.35 (s, 1H, H-2), 11.88 (br s, 1H, H-1). C-13 Nmr (DMSO-d_6, 75 MHz): 42.5, 45.3, 104.1, 136.3, 150.3, 163.2.

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14. Proton nmr of **6b** (DMSO-d_6): 3.45 (t, J = 4 Hz, 2H, NHC<u>H</u>$_2$CH:N), 5.59 (s, 2H, PhC<u>H</u>$_2$), 7.15 - 7.38 (complex, Ph), 7.85 (t, J = 4 Hz, 1H, NHCH$_2$C<u>H</u>:N), 7.95 (br t, J = 4 Hz, 1H, N<u>H</u>CH$_2$CH:N), 8.09 (s, 1H, H-2).
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